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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,684	12/14/1999	REINER LAUS	7636-0020.30	4142

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/461,684	LAUS ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

8.0.0

DETAILED ACTION

1. Applicant's amendment filed 5/9/05 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I (claims 1-7) and species of SEQ ID NO: 6.

Claims 1 and 4-7 read on the elected species, SEQ ID NO: 6.

Claims 1 and 4-7 are currently being examined to the extent they read upon the elected species SEQ ID NO: 6.

In view of Applicant's amendment filed 5/9/05, the following rejection remains.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(a) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1 and 4-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Buschle et al (PNAS USA 94: 3256-3261, 4/1997, IDS reference) in view of Kim et al (J. Immunol. 159(4): 1666-1668, 8/1997, previously provided).

Buschle et al teach that polycationic amino acids have been employed to enhance transport of proteins into cells and teach the ability of different cationic polymers, two of which are poly-Arg and poly-Lys, to transfer peptides to APCs (especially Abstract). Buschle et al teach compositions comprising antigenic peptides from pathogens and tumors and further comprising poly-Lys or poly-Arg (especially Abstract, Table 1 and page 3258, column 2 first full paragraph). Buschle et al teach that strongly augmented enhancement is only obtained with polyArg chains of 20 residues or more, that in practice, polyArg chains of at least 15 amino acid residues are required for enhancing peptide delivery to cells. Buschle et al teach that polyArg is more efficient than polyLys

at the same chain length (especially page 3259 at column 2). Buschle et al further teach that polyArg appears to act via an internalization-dependent mechanism, whereas polyLys appears to utilize permeabilization of the cell membrane (especially page 3261).

Buschle et al do not teach a composition comprising an antigen having an added peptidic sequence, wherein the added peptidic sequence is linked or fused to the said antigen.

Kim et al teach that because exogenous proteins do not ordinarily enter the cytosol [of APC] and access the MHC class I-processing pathway, protein-based vaccines that induce class I-restricted CTL responses have proved difficult to design. Kim et al further teach that they have addressed this problem by conjugating OVA antigen to a cationic peptide derived from HIV-1 tat which has a cysteine at the carboxy terminal end, and teach administration of a composition comprising the antigen/cationic peptide to APC leads to processing and presentation of the peptides in association with Class I MHC (especially Abstract). Kim et al teach that loading of the OVA-tat required cytosolic proteolysis and transport of peptide into the ER (especially page 1667 at the second column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an N-terminal cysteinylated peptide (as taught by Kim et al) version of the cationic poly-Lys peptide taught by Buschle et al and to have conjugated it to one of the antigens taught by Buschle et al (or Kim et al) as taught by Kim et al for the antigen/cationic peptide of Kim et al, i.e., to have fused or linked the two components of the composition taught by Buschle et al in a single polypeptide via a cysteine residue as per the teaching of Kim et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to do this to enhance the transport of proteins or peptides from pathogens or tumors into the class I processing pathway and to stimulate CTL responses because Kim et al teach that protein-based vaccines that induce class I-restricted CTL responses have proved difficult to design and conjugation of an antigen to a cationic peptide leads to class I MHC processing and presentation, Buschle et al teach that polycationic amino acids have been employed to enhance transport of proteins into cells, the ability of different cationic polymers, two of which are poly-Arg and poly-Lys, to transfer peptides to APCs, and compositions comprising antigenic peptides from pathogens or tumors and further comprising poly-Lys or poly-Arg. Claim 5 is included in this rejection because claimed recitation of intended use in immunizing a subject against a tumor or pathogen wherein the antigen is specific to the tumor or antigen does not carry any patentable weight per se. A compound is the same compound irrespective of its intended use. Claim 7 is included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in this product claim.

Applicant's arguments in the amendment filed 5/9/05 have been fully considered but are not persuasive.

Applicant's position is of record on pages 3-8 at section III in the said amendment, briefly that Kim et al teach away from he claimed invention because Kim et al teach that the result of enhanced APC uptake of antigenic peptide is specific to conjugating the antigenic peptide with tat, and that conjugating the antigenic peptide with polyLys does not work, and the combination represents an "obvious to try" situation.

It is the Examiner's position that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention for the reasons enunciated in the instant rejection and for those that follow.

Buschle et al teach that using polyArg or polyLys in combination with proteins or tumor-associated peptides enhances transport of the proteins or peptides into APC, and that a chain length of at least 15-20 Arg for polyArg was required for such enhanced delivery. Buschle et al further teach that polyArg was more efficient at the same chain length than polyLys, but that both were very efficient for enhanced delivery, so that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed invention with a reasonable expectation of success, i.e., to have used polyLys at at least 15-20 Lys residues in length or longer. Thus, Buschle et al teach that the 15-20-mer polyArg and polyLys have the desired APC uptake enhancing capability. It is the Examiner's further position that Kim et al teach away from using a 9-mer polyLys peptide, and although they concluded that a polyLys peptide of equal length was insufficient for transport, Buschle et al teach that a longer polyLys peptide does possess the desired transport function. In addition, Kim et al teach administration of a fusion or conjugate peptide comprising the antigenic peptide coupled to a cysteinylated cationic sequence, either the tat peptide or the polyLys peptide, rather than as a mixture of the cationic peptide and the antigenic peptide. It is the Examiner's position that one of ordinary skill in the art at the time the invention was made would have been motivated to prepare a cysteinylated peptide and to have coupled or fused it to the antigenic peptide such as taught by Kim et al for administration, and further because conjugation or fusion would target both components of the coupled or fused polypeptide to the same cell.

Applicant's remarks and newly disclosed information in Applicant's amendment filed 5/9/05 has necessitated the following new grounds of rejection.

5. Claims 1 and 4-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Buschle et al (PNAS USA 94: 3256-3261, 4/1997, IDS reference) in view of U.S. Patent No. 4,772,547.

Buschle et al teach that polycationic amino acids have been employed to enhance transport of proteins into cells and teach the ability of different cationic polymers, two of which are poly-Arg and poly-Lys, to transfer peptides to APCs (especially Abstract). Buschle et al teach compositions comprising antigenic peptides from pathogens and tumors and poly-Lys or poly-Arg (especially Abstract, Table 1 and page 3258, column 2 first full paragraph). Buschle et al teach that strongly augmented enhancement is only obtained with polyArg chains of 20 residues or more and that thus in practice, polyArg chains of at least 15 amino acid residues are required for enhancing peptide delivery to cells. Buschle et al teach that polyArg is more efficient than polyLys at the same chain length (especially page 3259 at column 2). Buschle et al further teach that polyArg appears to act via an internalization-dependent mechanism, whereas polyLys appears to utilize permeabilization of the cell membrane (especially page 3261).

Buschle et al do not teach a composition comprising an antigen having an added peptidic sequence, wherein the added peptidic sequence is linked or fused to the said antigen.

U.S. Patent No. 4,772,547 discloses vaccine compositions comprising antigenic peptides or proteins from hepatitis surface antigen and HIV envelope and adjuvants such as IFN, IL-2, thymosin alpha 1 (i.e., immunopotentiating proteins) (especially column 8 at lines 25-49). U.S. Patent No. 4,772,547 further discloses enhancing immunogenicity of the peptides by coupling the peptides covalently via Cys, i.e., by "crosslinking" to toxoids or carrier materials that enhance immunogenicity, said linking being either at the amino or carboxy terminus of the antigenic peptide (especially "Description of the Invention" section).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have cross-linked the 20-mer polyLys or polyArg immunogenicity enhancing cationic peptide taught by Buschle et al to an antigenic peptide such as one taught by Buschle et al and used in combination with the cationic peptide in the composition by Buschle et al, said cross-linking via Cys as disclosed by U.S. Patent No. 4,772,547 for the conjugates disclosed by U.S. Patent No. 4,772,547 that comprise antigenic peptides and immunogenicity enhancing polypeptides, i.e., to have fused or linked both components of the composition of Buschle et al in a single polypeptide (the polyLys or polyArg peptide linked or fused via Cys to the antigenic peptide).

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to initiate an effective immune response using the 20-mer cationic polyArg or polyLys taught by Buschle et al that has the high efficacy in enhancing peptide delivery to cells and crosslinking it via the Cys taught by U.S. Patent No. 4,772,547.

6. Claims 1 and 4-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Buschle et al (PNAS USA 94: 3256-3261, 4/1997, IDS reference) in view of WO 90/11092 A1, U.S. Patent No. 5,831,016 and U.S. Patent No. 4,772,547.

Buschle et al teach that polycationic amino acids have been employed to enhance transport of proteins into cells and teach the ability of different cationic polymers, two of which are poly-Arg and poly-Lys, to transfer peptides to APCs (especially Abstract). Buschle et al teach compositions comprising antigenic peptides from pathogens and tumors and poly-Lys or poly-Arg (especially Abstract, Table 1 and page 3258, column 2 first full paragraph). Buschle et al teach that strongly augmented enhancement is only obtained with polyArg chains of 20 residues or more and that thus in practice, polyArg chains of at least 15 amino acid residues are required for enhancing peptide delivery to cells. Buschle et al teach that polyArg is more efficient than polyLys at the same chain length (especially page 3259 at column 2). Buschle et al further teach that polyArg appears to act via an internalization-dependent mechanism, whereas polyLys appears to utilize permeabilization of the cell membrane (especially page 3261).

Buschle et al do not teach a composition comprising an antigen having an added peptidic sequence, wherein the added peptidic sequence is linked or fused to the said antigen.

WO 90/11092 A1 teaches that use of synthetic peptide vaccines is not effective because the peptides do not readily associate with MHC molecules, have a short serum half-life, are rapidly proteolyzed, or do not specifically localize to APC, and in addition, these exogenously administered antigens must compete with the universe of self-proteins for binding to APC (especially page 4 at lines 23-30).

U.S. Patent No. U.S. Patent No. 4,772,547 discloses vaccine compositions comprising antigenic peptides or proteins from hepatitis surface antigen and HIV envelope and adjuvants such as IFN, IL-2, thymosin alpha 1 (i.e., immunopotentiating proteins) (especially column 8 at lines 25-49). U.S. Patent No. 4,772,547 further discloses enhancing immunogenicity of the peptides by coupling the peptides covalently via Cys, i.e., by "crosslinking" to toxoids or carrier materials that enhance immunogenicity, said linking being either at the amino or carboxy terminus of the antigenic peptide (especially "Description of the Invention" section).

U.S.Patent No. 5,831,016 discloses that antigenic peptides may be linked to helper peptides (especially Table A at column 7).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have cross-linked the 20-mer polyLys or polyArg immunogenicity enhancing/APC delivery helper cationic peptide taught by Buschle et al to an antigenic peptide such as one taught by Buschle et al, U.S.Patent No. 5,831,016 or WO 90/11092 A1, said cross-linking via Cys as disclosed by US Patent No. 4,772,547 for the conjugates disclosed by US Patent No. 4,772,547 that comprise antigenic peptides and immunogenicity enhancing polypeptides, i.e., to have fused or linked both components of the composition of Buschle et al in a single polypeptide or to have linked the cationic peptides of Buschle et al to the antigenic peptide disclosed by U.S.Patent No. 5,831,016 or by WO 90/11092 A1 (the polyLys or polyArg peptide linked or fused via Cys to the antigenic peptide).

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to initiate an effective immune response using the 20-mer cationic polyArg or polyLys taught by Buschle et al that has the high efficacy in enhancing peptide delivery to APC because WO 90/11092 A1 teaches that use of synthetic peptide vaccines is not effective in part due to problems antigenic peptides not associating with APC, competing with self proteins for binding to APC, not being readily bound to MHC molecules on APC, and being rapidly proteolyzed, Buschle et al's cationic peptide enhances delivery of the antigenic peptide to APC as well as extending the length of the peptide for improved stability with regard to proteolysis, U.S.Patent No. 5,831,016 discloses that antigenic peptides may be linked to helper peptides, and U.S. Patent No. U.S. Patent No. 4,772,547 discloses that antigenic peptides may be linked via Cys to immunogenicity enhancing polypeptides.

7. It is noted by the Examiner that claim 6 has a spelling error at line 2, i.e., "sequences" should be "sequence".

8. No claim is allowed.

9. Applicant's remarks and newly disclosed information in Applicant's amendment filed 5/9/05 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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